CASE I: MLP12093 (JPC 4035110).

Signalment: 14-week-old male Sprague Dawley rat (*Rattus norvegicus*).

History: This rat was a clinically normal animal in an experimental drug study.

Gross Pathology: Both kidneys were moderately enlarged and when sectioned contained multiple, variably-sized (up to 3.0 mm diameter), fluid-filled spaces involving most of the renal parenchyma. The liver was slightly enlarged and had an irregular surface (Figure 1), which corresponded with spaces, similar to those seen in the kidneys, when sectioned. There were no gross abnormalities in other organs or tissues.

Laboratory Results: Routine hematology and clinical chemistry analysis were within normal limits.

Histopathologic Description: Kidney: Both the cortex and the medulla contained numerous dilated tubules lined by variably squamous to cuboidal to columnar epithelium (cysts), with rare papillary projections. Many of these cysts were distended by pale amphophilic fluid admixed with necrotic cellular debris, scant macrophages, and/or degenerate neutrophils. Between the cysts, some areas of the interstitium were expanded by loose connective tissue which often contained a few residual tubules of relatively normal caliber and/or a mixed inflammatory cell infiltrate. Occasional glomeruli had a slightly thickened basement membrane and the urothelium was slightly thickened.

Liver: There are multiple individual to coalescing spaces that were lined by variably attenuated cuboidal epithelial cells (cysts) and surrounded by a band of collagenous tissue. In the adjacent hepatic parenchyma, there was slight atrophy of hepatic cords, proliferation of bile ducts, and minimal mixed inflammatory cell infiltrate in periportal regions.

Contributor’s Morphologic Diagnosis: 1. Kidney: Severe multifocal renal tubular dilatation and ectasia with mild interstitial fibrosis.

2. Liver: Marked multifocal biliary duct hyperplasia and ectasia with mild portal fibrosis.
Contributor’s Comment: The gross and histopathologic findings in the kidney and liver are consistent with congenital polycystic kidney disease (PKD). PKD is a cystic genetic disorder of the kidneys which has been associated with cystic bile ducts, bile duct proliferation, and/or cystic pancreatic ducts.

In humans, there are two types of PKD: autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). In the more common form, ADPKD, the parenchyma is extensively replaced by cysts that originate from all segments of the nephron, collecting tubules, and ducts. In humans with ADPKD, there is an association with cysts in other organs, most often the liver. Other abnormalities that can be coupled with ADPKD include: cardiac valvular anomalies, intracranial aneurysms, and colonic diverticula. In ARPKD, cysts arise from only dilated collecting tubules and ducts and in most cases there is also biliary dysgenesis and hepatic fibrosis.1,3

In veterinary medicine, PKD has been recognized in many species including horses, pigs, lambs, calves, dogs, cats, and rodents. In domestic animals, PKD is most often consistent with ARPKD in that the disease manifests as stillbirths or death within the first few weeks of life due to renal failure. Syndromes resembling both recessive and dominant PKD have been described in domestic dogs and cats.4,7

Caroli’s disease is a rare inherited disorder characterized by dilation of the intrahepatic bile ducts which is associated with liver failure and polycystic kidney disease. In the simple form, only bile ducts are affected. The more complex form, also known as Caroli Syndrome, is also linked with portal hypertension and congenital hepatic fibrosis. The differences between the causes of the two forms have not yet been discovered.2,9

Recently, a PKD rat, which is a spontaneous mutant derived from a colony of crj:CD rats, was found to also have polycystic lesions in the liver. Because this may represent an animal model of Caroli’s disease, it has been well characterized and studied as a model of ADPKD. The mutation arose spontaneously, and initial analysis indicated inheritance as an autosomal recessive trait.2,8

The findings presented in this write up describe a case of polycystic kidney disease in a Sprague Dawley rat with involvement of the liver. The involvement of multiple organs suggests that the lesions resulted from a genetic or developmental process rather than an acquired process. Furthermore, the subclinical nature of the disorder and the large size of the kidneys at the time of necropsy suggest that the renal disease was progressive in nature.

2. Liver, bile ducts and ductules: Ectasia, diffuse, moderate to severe, with biliary ductular reaction.

Conference Comment: Polycystic kidney disease is a label used to refer to several pathologic entities, including incidental renal cysts and hereditary, developmental or acquired renal cysts. Four major mechanisms of cyst formation include: 1) obstruction of nephrons with increased intraluminal pressure and subsequent dilation, 2) changes in ECM and cell-matrix interactions
resulting in a weakened renal tubular basement and the formation of saccular dilations of the tubules, 3) disordered growth of tubular epithelial cells leading to focal hyperplastic lesions and cyst formation, and 4) dedifferentiation of tubular epithelial cells with loss of cell polarity, abnormal tubular arrangement, decreased tubular absorption and dilation of tubules. Often, several of these mechanisms occur concurrently to create renal cysts.\textsuperscript{7} Incidental renal cysts, which do not cause renal dysfunction, are fairly common in pigs and calves.\textsuperscript{4} Interstitial fibrosis or intratubular obstruction can result in acquired renal cysts (as well as hydronephrosis), which generally arise within the renal cortex.

In contrast, polycystic kidneys contain numerous cysts involving multiple nephrons.\textsuperscript{7} In veterinary species, inherited PKD can be autosomal dominant or autosomal recessive; lesions are generally bilateral and cysts may affect any part of the nephron. ADPKD is described in bull terrier dogs and adult Persian cats. It can affect both proximal and distal convoluted tubules and typically results in chronic nephritis and renal failure.\textsuperscript{4} ADPKD may be associated with mutations of PKD1 and/or PKD2 genes, which result in defective polycystin 1 and/or polycystin 2, respectively.\textsuperscript{4} Polycystin 1 is a component of desmosomes that is important in cell adhesion and signaling; its loss may ultimately result in impairment of normal tubulogenesis.\textsuperscript{7} Polycystin 2, on the other hand, functions as a plasma membrane calcium channel.\textsuperscript{7} ARPKD, reported in Persian kittens, sheep, lambs, and West Highland white and cairn terrier puppies, is caused by a mutation on the PKHD1 gene encoding fibrocystin, which is a receptor protein.\textsuperscript{5} In adult Persian cats and West Highland white terrier puppies with PKD, there are often concurrent hepatic cysts.\textsuperscript{4} Congenital PKD, with inheritance that is not fully characterized, occurs in pigs, lambs, calves, kids, puppies, kittens and foals. The most common manifestation of this condition is stillbirth or neonatal/infant death.\textsuperscript{5}

PKD has also been reported in Brazilian agoutis (Dasyprocta leporina), springboks (Antidorcas marsupialis), an adult raccoon (Procyon lotor), rhesus macaques (Macaca mulatta), slender lorises (Loris lydekkerianus), and a stillborn white-tailed deer (Odocoileus viriginianus).\textsuperscript{5} Two separate conditions resulting in polycystic kidneys are reported in goldfish. Infection with the myxosporidian protozoan Mitraspora cyprini causes a condition known as “kidney bloater disease,” characterized by marked renal tubular hyperplasia and ectasia, with sparing of the glomeruli. Conversely, goldfish polycystic kidney disease primarily involves glomeruli. It is distinguished by severe dilation of the subcapsular space, with the thin connective tissue wall of Bowman’s capsule overlying a layer of squamous parietal epithelium. The etiology of this lesion is unknown.\textsuperscript{6}

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CASE II: KM07/13A342 (JPC 4032702).

Signalment: Full term fetus, male rhesus macaque (*Macaca mulatta*).

History: Found dead.

Gross Pathology: Male fetus presented with swollen face and extremities. Dystocia suspected. Both testicles were intra-abdominal. The left testicle was swollen, cystic, and measured 1.5x2cm.

Histopathologic Description: The polycystic mass is composed of variably sized, fluid-filled cysts with a thin outer rim of immature testis and solid areas with mature ectodermal and endodermal structures. At the periphery, clusters of seminiferous tubules with a single and multiple layers of Sertoli cells are located around cuboidal cell-lined channels of the rete testis. Protein filled cysts are lined by single and sometimes multiple layers of keratinized squamous to cuboidal epithelium.

Ectodermal components include scattered nests of squamous epithelium with peripheral basal layers, central stratum lucidum, and inner stratum corneum and a central keratin core. Some sections contain haired skin with keratinized epidermis, hair follicles and shafts, dermal vasculature and fat, and clusters of adnexal glands. Mesodermal components include scattered islands of cartilage, rare spicules of new bone formation, and rudimentary tooth formation. Endodermal components consist of cystic spaces lined by complex cuboidal to columnar epithelium mixed with goblet cells that cover papillary villous-like projections and has a submucosa with lymphoid aggregates.
**Contributor’s Morphologic Diagnosis:** Testis: Teratoma.

**Contributor’s Comment:** Neoplasia of the gonad in non-human primates is extremely rare. In our colony we have only seen three teratomas (one testicular and two ovarian), a dysgerminoma, and one interstitial cell tumor over the last 25 years.

Teratomas of the human testis can be classified as solid or cystic, and mature or immature, based on whether components have adult or embryonic features; the tumors often have features of both. In animals, teratomas are most frequently found in the horse, the majority in cryptorchid testes. In the fetus, teratoma formation probably prevents normal descent. Human cases with undescended testes are 5-48 times more likely to be neoplastic, but neoplasia after surgical reduction (orchiopexy) and in the other normally descended testis is also reported.

In animals most teratomas are benign, as are most ovarian teratomas in women, whereas most post pubertal testicular tumors in men are malignant (except those occurring in childhood), suggesting origin from benign and malignant cells respectively. The difference may be based on the human female’s tolerance for parthenogenetic development of immature somatic ova cells into three germ layers while suppressing neoplastic cells, in contrast to the human male that differentiates malignant immature somatic cells less efficiently in the embryo. Why this hypothesis does not appear to extend to animals is unexplained.

**JPC Diagnosis:** Testis: Teratoma.

**Conference Comment:** Totipotential primordial germ cells can give rise to several types of tumors, including relatively undifferentiated embryonal carcinomas, and more differentiated yolk sac tumors and choriocarcinomas. Additionally, they may differentiate along somatic cell lines to form teratomas. The term “teratoma” is derived from the Greek word “teraton” meaning “a monster.” These tumors are classically defined as having at least two of the three embryonic layers (i.e., endoderm, mesoderm, and ectoderm), however, recent classifications also include monodermal types. See Table 1 for the tissue derivatives of these embryonic layers. Teratomas have been reported in horses, cattle, dogs, mice, ferrets and some wildlife species, such as roe deer, a giraffe and a great blue heron. They occur most frequently in the gonads; however, these tumors can also develop at extragonadal locations, usually along the midline. The most plausible rule-out for a well differentiated teratoma is a dermoid or epidermoid cyst. Both are benign, cystic tumors, lined by stratified squamous epithelium and often filled with lamellations of keratin; however, the dermoid cyst may also produce adnexal structures such as hair follicles, sebaceous glands, and sweat glands (see WSC 2013-14, conference 1, case 1).

For comparison to the testicular teratoma, conference participants examined a mouse ovarian teratoma, provided by the moderator. The ovarian teratoma was composed of haphazard regions of neuroectoderm, vague glandular/ductular components, poorly differentiated muscle (mesoderm) and respiratory epithelium (endoderm), consistent with an immature teratoma.

Table 1: Embryonic germ cell layers and selected tissue derivatives.
<table>
<thead>
<tr>
<th>Ectoderm</th>
<th>Mesoderm</th>
<th>Endoderm</th>
</tr>
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<tbody>
<tr>
<td>• Epidermis of skin and its derivatives (sweat glands, hair follicles,</td>
<td>• Notochord</td>
<td>• Epithelial linings (digestive tract, respiratory system,</td>
</tr>
<tr>
<td>and sensory receptors)</td>
<td>• Musculoskeletal system</td>
<td>urethra, urinary bladder, and reproductive system)</td>
</tr>
<tr>
<td>• Epithelial lining of mouth and anus</td>
<td>• Muscular layer of stomach and intestine</td>
<td>• Liver</td>
</tr>
<tr>
<td>• Cornea and lens of eye</td>
<td>• Excretory system</td>
<td>• Pancreas</td>
</tr>
<tr>
<td>• Nervous system</td>
<td>• Circulatory and lymphatic systems</td>
<td>• Thymus</td>
</tr>
<tr>
<td>• Adrenal medulla</td>
<td>• Reproductive system (except germ cells)</td>
<td>• Thyroid and parathyroid glands</td>
</tr>
<tr>
<td>• Tooth enamel</td>
<td>• Dermis of skin</td>
<td></td>
</tr>
<tr>
<td>• Epithelium of pineal and pituitary glands</td>
<td>• Adrenal cortex</td>
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</tbody>
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**References:**


**CASE III: MK12-3255 (JPC 4036188).**

**Signalment:** 17-year-old male rhesus macaque (*Macaca mulatta*).

**History:** In 1998, the macaque underwent total body irradiation followed by autologous bone marrow transplantation to track the development of peripheral blood cells from retrovirus-marked stem cells. The bone marrow was successfully engrafted and the macaque was considered to be immunocompetent. Fourteen years later, the animal presented acutely with coughing and hemoptysis and was sedated for evaluation. The animal was in thin body condition with pale mucous membranes. Lung sounds were judged to be harsh but heart sounds were normal. Radiographs revealed consolidation of the left lung field and aerophagia of the esophagus and stomach. The monkey was subsequently euthanized.

**Gross Pathology:** The left lung lobes were consolidated and diffusely and firmly adhered to the pleural wall. Within the cranial left thoracic cavity, there was a small amount of thin, serosanguineous fluid. When the left lung lobes were incised, there was abundant, red/brown/dark yellow viscous fluid. There were yellow nodular areas (abscesses) in the caudal left lung lobes. The right lung lobes also were consolidated but not as severely as the left and, when incised, also had viscous fluid. Samples of the pleural fluid, abscesses and consolidated lung were collected for bacterial culture. The mediastinal, sternal and thoracic lymph nodes were moderately - markedly enlarged. Sections of lung and tracheobronchial lymph nodes were collected for PCR for mycobacterium. No other significant gross changes were noted.

**Laboratory Results:**

- *Klebsiella pneumoniae* was cultured from the pleural effusion, one of the nodules and a section of left lung lobe.
- Sections of lung and thoracic lymph nodes were negative for *Mycobacteria sp.* by PCR.
- Gram stain revealed numerous gram-negative rods.
- Fungal cysts, consistent with *Pneumocystis* spp., were not found with GMS stain.
- *Mycobacteria* spp. were not seen with Acid Fast stain.

**Histopathologic Description:** Lung: Bronchi contained neutrophils and macrophages admixed with extra and intracellular bacterial rods. Alveoli were lined by hypertrophied type II pneumocytes and were expanded by numerous neutrophils, macrophages with fewer multinucleate giant cells. Within macrophages and multinucleate giant cells, the bacteria were surrounded by clear spaces (capsule). Connective tissue around bronchi was edematous with fibrin deposition and scattered inflammatory cells. There was pleuritis composed of small aggregates of neutrophils, bacteria and fibrin.
Contributor’s Morphologic Diagnosis: Lung: Bronchopneumonia multifocal and focally extensive, suppurative, moderate – marked, acute with gram-negative rods and mild pleuritis.

Contributor’s Comment: Other lesions included:
- Pancreas islet cell hyalinization, multifocal, mild
- Heart, myocardial degeneration, loss and fibrosis, multifocal, minimal - mild
- Kidney, cyst, focal, mild
- Lymph node, lymphoid hyperplasia, moderate

*Klebsiella pneumoniae* is a gram-negative, non-spore-forming, facultative, anaerobic, nonmotile rod with a prominent capsule. Non-pathogenic strains can be found in soil, water, man and mammals; the bacteria colonize mucosal surfaces. *Klebsiella pneumoniae* afflicts the debilitated, immunosuppressed and those in hospitals and long-term care facilities and is the most frequent case of gram-negative pneumonia. Intravenous catheters and surgical sites may also serve as sources of infection.\(^4,10,13\)

Disease in nonhuman primates may be associated with such stressors as shipping, quarantine and overcrowding. In New World monkeys and Old World monkeys, *Klebsiella pneumoniae* infection has been associated with septicemia, air sacculitis, pneumonia, pulmonary abscess, peritonitis, cystitis and meningitis. Vaccination with killed whole bacterin in owl monkeys, capsular polysaccharide in squirrel monkeys, and autogenous vaccines in marmosets have been used to reduce morbidity and mortality due to *Klebsiella pneumoniae* infection.\(^14\)

*Klebsiella pneumoniae* in lab animals is a rare cause of enterotyphlitis, septicemia and necrotizing bronchopneumonia in rabbits; septicemia, bronchopneumonia, pericarditis, pleuritis and peritonitis in guinea pigs; lymph node and kidney abscesses as well as rhinitis in rats. In mice, cervical lymphadenopathy, liver and kidney abscesses, empyema, endo- and myocarditis and thrombosis are associated with, but not diagnostic for, *Klebsiella pneumoniae* infection.\(^6,7,8,9\) In domestic animals, *Klebsiella pneumoniae* has been isolated from mares with endometritis and abortion and from foals with pneumonia and septicemia.\(^2,12\)

A hypermucoviscous (HMV) variant of *Klebsiella pneumoniae* (HMV-KP) has been identified in humans and subsequently in animals. The virulence of HMV is thought to be due, in part, to capsular serotypes (K1 and K2) that carry genes MagA (mucoviscosity-associated gene/K1 specific capsular polymerase gene) and rmpA (regulator of mucoid phenotype) which make the bacteria more invasive and more resistant to phagocytosis.\(^13,15\) Bacterial colonies appear mucoid and have a positive string test (an inoculation loop is pulled through the bacterial colony and the resulting string formed is greater than 5mm). In humans, HMV infection is unusual in that it infects healthy individuals and causes liver abscesses, pneumonia, meningitis, and endophthalmitis. The mode of infection is unknown but is thought to be via the intestine.\(^12,13\)

*Klebsiella pneumoniae* with an HMV phenotype has been identified in African green monkeys in which abscesses were found in the abdomen, lungs, cerebellum and skin. The masses appeared to be centered on lymph nodes and there was associated peritonitis and adhesions to the intestines. Oral and rectal swabs of macaques in the same facility identified animals that were subclinically infected.\(^1,16\)
Klebsiella pneumoniae HMV has been cultured from California sea lions dying shortly after being observed to be ill. Many of the animals were in good body condition but had bronchopneumonia, fibrinous pleuritis and abscess. Sea lions may serve as a potential source of zoonotic disease for swimmers.5

The HMV phenotype can be detected by rapid real-time PCR assays that target rmpA and magA genes. RAPD (rapid amplification of polymorphic DNA) can then be used to determine genetic variability between isolates.3

**JPC Diagnosis:** Lung: Bronchopneumonia, suppurative, multifocal to coalescing, severe, with numerous intra- and extracellular bacilli.

**Conference Comment:** The contributor provides an excellent summary of Klebsiella pneumoniae infection in humans and veterinary species. Klebsiella can affect a variety of organ systems, including the respiratory and urinary tracts, which differ considerably with respect to host defense mechanisms. As a result, virulence factors can differ between bacterial strains. Current research has demonstrated important pathogenicity factors of Klebsiella spp. including the polysaccharide capsule, the lipopolysaccharide O antigens, pili/fimbriae, and siderophores.10

The polysaccharide capsule is essential for Klebsiella virulence. It prevents phagocytosis, suppresses the activation of complement components (especially C3b), and may inhibit macrophage differentiation.10 Klebsiella spp. have developed resistance to the host serum bactericidal effect, normally mediated by complement proteins. This resistance likely involves two factors: 1) capsular polysaccharide, which may mask LPS and prevent complement activation and 2) the structure of lipopolysaccharide (LPS). It is hypothesized that the O antigens of LPS extend through the capsule layer, where complement protein C3b is fixed preferentially to the longest O-polysaccharide side chains. This binding fixes C3b far enough away from the bacterial cell membrane that the formation of the lytic membrane attack complex (C5b–C9) is prevented.10 Pili, or fimbriae, are nonflagellar, filamentous bacterial surface projections that act as adhesions to bind host cells. Type 1 pili mediate bacterial colonization of mucus or epithelial cells of the urogenital, respiratory, and intestinal tracts, while type 3 pili adhere to endothelial cells, respiratory and urinary epithelium, tubular basement membranes, Bowman’s capsules, and renal vessels.10 Finally, since iron availability is a limiting factor for bacterial growth, Klebsiella spp. secrete siderophores, such as enterobactin and aerobactin. Siderophores are high-affinity, low-molecular-weight iron chelators that are capable of competitively taking up iron bound to host proteins.10

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**References:**


CASE IV: MK12-557 (JPC 4036187).
**Signalment:** 6-year-old male rhesus macaque (*Macaca mulatta*).

**History:** This macaque was inoculated intravascularly with SHIV in April 2010. The macaque tested negative for Herpes B, measles virus, SRV, STLV-1, and SIV one year prior to experimental infection. The macaque was relatively healthy for approximately 2 years post-infection, but several months prior to necropsy developed a nasal discharge and was treated with antibiotics over this period. The macaque became acutely hypoactive and lethargic and euthanasia was performed.

**Gross Pathology:** The macaque was somewhat thin but relatively well muscled and contained a small amount of body fat. Within the pinna of the left ear, there was a focal area of ulceration with a superficial scab measuring approximately 1.5 cm in diameter. There was a focal slightly elevated tan-white lesion measuring approximately 1 cm in greatest dimension on the tip of the left side of the tongue. The remainder of the tongue and oral cavity appeared normal.

The mesenteric lymph node was severely enlarged and measured 5.0 x 3.5 x 2.0 cm, and was tan to white on cut surface. A focal tan-white lesion was present within the jejunum with prominent thickening of the wall over a length of 4.5 cm. The colonic and pancreatic lymph nodes were moderately enlarged. The spleen was mildly enlarged and there were multiple nodules within the parenchyma which were irregular, tan-white and up to 1.5 cm in diameter. The wall of the gallbladder was moderately to severely thickened and was white to tan. These lesions were consistent with lymphoma.

The heart, kidneys, stomach, duodenum, ileum, cecum, colon and testes appeared normal. Several adhesions were present between the right caudal lung lobe and thoracic wall. The lungs otherwise appeared grossly normal.

**Laboratory Results:** Total lymphocyte counts averaged 1145/μL over the last six months of life. CD4 counts were less than 200/μL over the same period. The macaque maintained a high level of viremia for SHIV during this period.

**Histopathologic Description:** The submitted slide is a section from the left ear pinna. The epidermis is focally ulcerated with an overlying serocellular crust, comprised primarily of degenerative neutrophils. The epidermis at the lateral margins of the lesion is irregular, with disarray and ballooning of epithelial cells, admixed with degenerative neutrophils. Many epithelial cells along the margin have enlarged nuclei with marginated chromatin and prominent amphophilic intranuclear inclusion bodies. Several syncytial cells are evident, containing intranuclear inclusions. Some of the adjacent sebaceous glands have similarly affected epithelium with cells containing prominent intranuclear inclusion bodies.

Examination of the tongue (not submitted) revealed an acute focal ulcerative glossitis with the margins of the lesion containing epithelial cells with prominent amphophilic intranuclear inclusion bodies. Transmission electron microscopy from a section of tongue revealed intranuclear icosahedral viral nucleocapsid particles measuring approximately 100 nm, and enveloped particles approximately 160 nm in diameter in the cytoplasm, consistent with herpesviral particles.
Other significant findings in this case included lymphoblastic lymphoma affecting the spleen, jejunum, gall bladder, adrenal gland, and mesenteric, perisplenic, pancreatic and colonic lymph nodes. Additionally, there was a granulomatous colitis and lymphadenitis affecting a portion of the colon and associated lymph nodes due to mycobacterial infection, with large numbers of acid fast bacilli evident in macrophages in the affected tissue. Mild to moderate multifocal interstitial pneumonia and fibrosis were evident in the lung.

**Contributor’s Morphologic Diagnosis:** External ear, otitis externa, acute, focal, ulcerative, with intranuclear inclusion bodies, consistent with alpha herpesvirus.

**Contributor’s Comment:** This macaque developed several disease conditions related to immunosuppression from experimental infection with SHIV. The principal presenting signs were upper respiratory and were likely related to the findings of pulmonary fibrosis and multifocal interstitial pneumonia. The macaque had lymphoma affecting multiple organs. Additionally, there was granulomatous colitis multifocally due to infection with mycobacteria. The findings of herpetic lesions involving the tip of the tongue and the left ear also reflect the ongoing immunosuppressive state in this macaque. The external pinna is an unusual location for active herpesviral infection, with the lingual lesion being more typical. No other lesions were noted systemically due to herpesviral infection. While the herpesviral infection is likely due to macacine herpesvirus-1 in this case, the possibility of infection with herpes simplex virus-1 cannot be ruled out. This macaque had tested previously negative by serology for herpes B and this may represent a false negative result. While the macaque may have become infected subsequent to experimental SHIV inoculation, this is less likely as these macaques were singly housed following inoculation.

Macacine herpesvirus-1, previously known as Cercopithecine herpesvirus-1, Herpes virus simiae and Herpes B virus is a common alpha herpesvirus infection affecting Old World macaques. It has been documented in rhesus macaques (*Macaca mulatta*), cynomolgus macaques (*M. fascicularis*), stump-tailed macaques (*M. arctoides*), pigtailed macaques (*M. nemestrina*), Japanese macaques (*M. fuscata*), bonnet macaques (*M. radiata*) and Taiwan macaques (*M. cyclopis*). Natural infection in macaques is usually asymptomatic, with localized mucosal lesions occurring infrequently. Transmission is horizontal between macaques with most animals acquiring the infection by 2-4 years of age. Lesions when present typically involve the oral and gingival mucosa, tongue and conjunctiva. Genital lesions are generally not observed. Infection of New World monkeys, while uncommon, is also possible. Asymptomatic natural infection with macacine herpesvirus-1 has been documented in a colony of brown capuchin monkeys (*Cebus apella*).^3^

Macacine herpesvirus-1 has typical morphology for alpha-herpesviruses and is composed of double stranded DNA, with a 40 nm core, icosahedral nucleocapsid approximately 100 nm in diameter and enveloped particles of 160-180 nm in the infected cell cytoplasm. Host cell infection occurs by fusion of viral envelope with host cell plasma membranes, penetration of nuclear pores by viral capsids with release of viral DNA in the nucleus, leading to viral replication.^6^
Transmission typically occurs via exposure of oral, ocular or genital mucous membranes from an infected animal shedding virus most commonly in saliva. The virus replicates locally, enters sensory nerves and is transmitted intra-axonally where it can remain latent in sensory ganglia, protected from host immune responses. Reactivation can occur periodically from the latent state, with virus being transported down axons to mucosal tissues. The majority of reactivated infections are asymptomatic. Virus carriers generally have a low rate of shedding, however, stress associated with transportation, changes in social groupings and immunosuppression can lead to reactivation and viral shedding.

While generally not a significant clinical disease entity for immunocompetent macaques, cases of systemic infection have been documented in cynomolgus macaques causing necrosis of lung, liver, spleen, pancreas, and adrenal glands. In one of these cases infection with Simian retrovirus type D was noted as the likely cause of immunosuppression leading to pathogenic herpesvirus infection.

Macacine herpesvirus is an extremely important zoonotic agent. Human exposure to an infected macaque shedding virus can result in a highly pathogenic infection leading to CNS involvement and a fatality rate greater than 70% in individuals who are not treated aggressively with antiviral drugs. Universal precautions with appropriate PPE are required when working with nonhuman primates. Any exposure by scratch, bite, needle stick injury or any other exposure of mucous membranes or an open skin wound require immediate attention and consultation with occupational medical specialists.

**JPC Diagnosis:** Haired skin, pinna: Dermatitis, necrotizing, multifocal, severe, with folliculitis, furunculosis, and numerous intraepithelial intranuclear viral inclusions and syncytia.

**Conference Comment:** The contributor has provided an excellent review of macacine herpesvirus-1. In addition to the section of ulcerated pinna, the contributor/moderator provided conference participants with the opportunity to examine multiple tissues from this animal, both microscopically and grossly (via photographs). Lesions in the tongue were similar to those described in the pinna, with focally extensive glossal ulceration, a marked neutrophilic infiltrate, large eosinophilic intra-nuclear inclusion bodies within epithelial cells and occasional viral syncytia. Transmission electron microscopy of the tongue was also consistent with α-herpesviral infection (see contributor’s histopathologic description). The spleen, liver, gallbladder, multiple lymph nodes and a focal area of the jejunum were grossly thickened/enlarged. Microscopically, these tissues were infiltrated by a monomorphic population of mononuclear cells with large nuclei and prominent nucleoli, interpreted as disseminated lymphoblastic lymphoma. Neoplastic lymphocytes demonstrated strong cytoplasmic immunoreactivity for anti-CD79a, suggesting B-cell origin, although there were scattered CD3-positive T-cells within the neoplasm. There was also marked granulomatous lymphadenitis and colitis. Several mesenteric lymph nodes and sections of colon were effaced by numerous epithelioid macrophages, with abundant intra-histiocytic acid-fast bacilli, consistent with *Mycobacterium avium*. Interestingly, despite this considerable microscopic evidence of mycobacteriosis, PCR for *Mycobacteria* spp. was negative.
Overall, this rhesus macaque had lymphoma, α-herpesviral glossitis and otitis externa, granulomatous lymphadenitis/colitis (likely secondary to *M. avium*) and alveolitis, interstitial pneumonia and fibrosis.

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